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(71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(72) Inventors: RAGHAVAN, Krishnaswamy, S.; 3 Hickory Court, Cranbury, NJ 08512 (US). RANADIVE, Sunanda, A.; 24 Agate Road, East Brunswick, NJ 08816 (US). GOUGOUTAS, Jack, Z.; 101 Westerly Road, Princeton, NJ 08540 (US). DIMARCO, John, D.; 16 Neal Drive, East Brunswick, NJ 08816 (US). PARKER, William, L.; 216 Hale Street, Pennington, NJ 08534 (US). DAVIDOVICH, Martha; 159 Fern Road, East Brunswick, NJ 08816 (US). NEUMAN, Ann; 615 South 7th St., Lafayette, IN 47901 (US).

(74) Agent: MORSE, David, M.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

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WO 02/22126 A1

(54) Title: GATIFLOXACIN PENTAHYDRATE

(57) Abstract: There are provided in accordance with the present invention crystalline gatifloxacin pentahydrate represented by the formula (I) in a highly homogeneous form with respect to other crystalline forms thereof.

GATIFLOXACIN PENTAHYDRATE

Cross Reference to Related Application

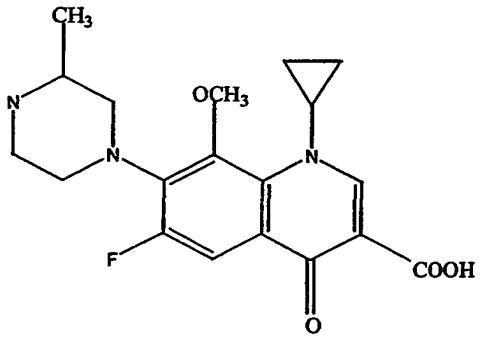
This application claims the benefit of U.S. Provisional Application Serial Number 60/232,293 filed on September 13, 2000.

Field of the Invention

The present invention relates to crystalline gatifloxacin pentahydrate and a process for producing it.

Background of the Invention

Gatifloxacin, chemically 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperizinyl)-4-oxo-3-quinolinecarboxylic acid, is represented by the following structure:



Gatifloxacin is a broad-spectrum quinolone antibiotic which is disclosed and claimed in U.S. Patent No. 5,043,450 as being isolated as the hemihydrate. U.S. Patent No. 5,880,283 discloses a sesquihydrate crystalline form of gatifoxacin that is disclosed as having advantages over the hemihydrate in pharmaceutical manufacturing. Such advantageous properties for the sesquihydrate in comparison to the hemihydrate include

enhanced stability under varying conditions of humidity and superior disintegration and dissolution rates of tablets made therefrom.

Both the hemihydrate and the sesquihydrate forms have demonstrated a definite tendency to form higher hydrates in the presence of water.

In accordance with the present invention, it has been found that gatifloxacin pentahydrate in highly homogeneous form is advantageous to previously known forms and can be utilized to prepare stable pharmaceutical dosage forms, including an aqueous suspension, because it is the most physically stable form and does not have a tendency over time to convert to another crystalline form.

Brief Description of the Drawings

FIG. 1 is an illustration of the interrelationship among the crystalline forms of gatifloxacin.

FIG. 2 shows the powder x-ray diffraction patterns of the pentahydrate and other crystalline forms of gatifloxacin.

FIG. 3 is a powder x-ray diffraction pattern of gatifloxacin pentahydrate.

FIG. 4 is a differential scanning calorimetry analysis of gatifloxacin pentahydrate.

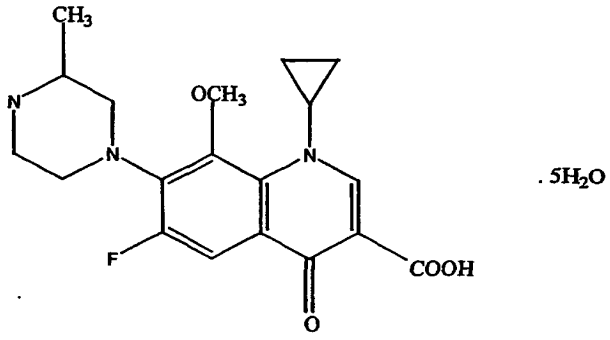
FIG. 5 is a thermogravimetric analysis of gatifloxacin pentahydrate.

Summary of the Invention

In accordance with the present invention, there is provided a crystalline gatifloxacin pentahydrate which is highly homogeneous in regard to other crystalline forms thereof and has superior properties in comparison to such other crystalline forms. The present invention further pertains to a process for the preparation of homogeneous gatifloxacin pentahydrate, pharmaceutical formulations containing it and the use thereof in the treatment of a wide variety of infections.

Detailed Description of the Invention

In accordance with the present invention, there is provided a novel highly homogenous crystalline pentahydrate form of the broad spectrum antibiotic gatifloxacin, 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid , represented by the following structure:



Gatifloxacin is approved for use as a broad spectrum antibacterial therapeutic agent. Gatifloxacin has been shown to be both safe and efficacious in the treatment of infections in individuals with impaired liver function. It has also been shown to be effective against a broad spectrum of microorganisms including antibiotic-resistant strains of *Streptococcus Pneumoniae* and to possess excellent overall tolerability.

The initial formulation process for the preparation of tablet dosage forms containing gatifloxacin sesquihydrate was a conventional wet granulation procedure. However, when a clinical batch of such tablets failed to conform to specifications, it was discovered by Differential Scanning Calorimetry that the pattern of the bulk material used in this batch was qualitatively different from that of the earlier small scale batches, and that this difference correlated with the failure of the tablets to meet performance specifications. Further investigation revealed a complex array of transformations involving a number of hydrated and anhydrous forms of the drug, principal among which were the sesquihydrate, the pentahydrate and the hexahydrate. In all, at least twelve different crystalline forms of gatifloxacin were identified and their interrelationships mapped as illustrated in FIG. 1.

The crystal structures and ideal water content of seven of these forms were established through single crystal x-ray analyses. Each form gives rise to unique and characteristic single crystal and powder x-ray diffraction. The kinetic and thermodynamic relationships among the three major hydrates were investigated leading to the understanding of their stability order in water as a function of temperature and their interconversion relationship. Further, the aqueous solubility relationship among them was found to parallel their thermodynamic stability order with the pentahydrate and sesquihydrate having the lowest and highest solubility at 25°C, respectively. The implications of these findings were very significant in the discovery and development of highly homogeneous gatifloxacin pentahydrate in accordance with the present invention. Further, these findings made it evident that very strict process controls were necessary in the production of crystalline gatifloxacin and dosage forms containing it and that it was necessary to obtain crystalline gatifloxacin pentahydrate in high homogeneity vs. the other crystalline forms in order to realize the advantageous properties thereof. By high homogeneity is meant that crystalline gatifloxacin pentahydrate must

contain no detectable levels of the other crystalline forms thereof as determined by powder x-ray diffraction technique.

Gatifloxacin pentahydrate is further characterized by crystal parameters obtained from single crystal x-ray crystallographic analysis as set forth below.

Single Crystal Parameters of gatifloxacin pentahydrate:

Cell dimensions

a=9.339(1) angstrom alpha= 106.55(2) degrees

b=13.556(3) angstrom beta= 91.93(1) degrees

c=9.269(1) angstrom gamma=100.44(1) degrees

V=1101.7(7) cubic angstrom

Space group: P1bar

Triclinic

Molecules/unit cell= 2

Density (calculated) (g/cubic cm)= 1.403

Crystalline gatifloxacin pentahydrate may be prepared in high homogeneity by transforming the crude sesquihydrate product as formed by the process taught in U.S. Patent No. 5,880,283. Gatifloxacin is initially crystallized from 90% ethanol as a highly solvated ethanolate (E in Fig. 1). The ethanolate desolvated to a crystalline product which approximates a hemihydrate (TE in Fig. 1). This product is rapidly transformed in water to the sesquihydrate (RP in Fig. 1) by heating to about 80°C and slowly transformed to the hexahydrate (H6 in Fig. 1) at room temperature over a longer period. Continued equilibration of the hexahydrate product in water at room temperature will produce the pentahydrate (H5 in Fig. 1). Alternatively, once the pentahydrate has been formed and isolated, it may be utilized as seed crystals for a more rapid process of forming it from the sesquihydrate (or any other form). In this process, a small quantity of the pentahydrate, i.e. from about 0.1% to 2% by weight based on the weight of the sesquihydrate, is

combined with the sesquihydrate (or any other crystalline form) and suspended in water with stirring at ambient temperature until conversion to the pentahydrate is completed, usually 24 hours or longer.

In addition to the crystalline forms of gatifloxacin described in the previous paragraph, other forms exist as illustrated in FIG. 1, which is a chart of the various forms and their process interrelations and FIG. 2, which shows the powder x-ray diffraction patterns of the various forms. In FIG. 1, the forms for which single crystal x-ray structures have been determined are indicated. Further, various equilibrium and kinetic transformations among the crystalline forms are indicated. The designations beginning with "T" indicate crystal forms produced by solid-solid transformations. Of the various crystalline forms of gatifloxacin, the primary ones that crystallize directly from aqueous solvents, as opposed to forms that crystallize from a molten phase or by solid-solid transformations, are the sesquihydrate, the hexahydrate and the pentahydrate.

Formation of the thermodynamically most stable form is a reasonable expectation for a solution mediated process, and using the most stable form rather than a metastable form is advantageous regarding physical stability of the crystalline form. The increased physical stability will afford additional advantages in formulation.

It has been found in accordance with the present invention that the advantageous stability and solubility properties of the pentahydrate of gatifloxacin can be applied to the formulation of pharmaceutical dosage forms. While the pentahydrate of gatifloxacin can be utilized to prepare tablets by wet granulation, it can also be formulated in accordance with the present invention into stable pharmaceutical solid dosage forms by conventional dry granulation. Stability studies on the pentahydrate form have demonstrated no evidence of form change or other degradation under stressed conditions of temperature and humidity, indicating that tablets made

by dry granulation using the pentahydrate form are expected to be stable. Such formulations will include conventional inert ingredients such as binders, excipients, disintegrants, and the like. Examples of such agents include various starch derivatives such as pregelatinized starch, hydroxypropyl cellulose microcrystalline cellulose, sodium starch glycolate, magnesium stearate, lactose, mannitol and the like.

The pentahydrate of gatifloxacin is also more appropriate for the preparation of aqueous dosage forms than the metastable sesquihydrate in spite of being less soluble. This is commercially significant since gatifloxacin has demonstrated excellent efficacy both parenterally and via oral administration. Such oral formulations are formulated as ready to use suspensions or packaged as a dry powder suitable to be suspended in an appropriate amount of water just prior to use. The powder could be prepared by any conventional technique recognized in the art, but would preferably be formulated by mixing the highly homogeneous crystalline gatifloxacin pentahydrate with the other ingredients in powder form and the mixture packaged in an appropriate container. The other ingredients utilized to formulate such preparations would include conventional inert ingredients such as microcrystalline cellulose, methyl cellulose and the like, suitable sweetening and/or flavoring agents, and preservatives therefor if required. Such solid oral dosage forms or dry formulations suitable for the preparation of suspensions would be formulated such that they would contain an effective dose of gatifloxacin. In general, solid dosage forms containing 200 mg or 400 mg of gatifloxacin are contemplated. Preparations suitable for oral suspension would contain a similar dosage.

It is understood that various other embodiments and modifications in the practice of the invention will be apparent to, and can be readily made by, those of ordinary skill in the art without departing form the scope and spirit of the invention as described above. Accordingly, it is not intended that the scope of the claims appended hereto be limited to the exact description set

forth above, but rather that the claims be construed as encompassing all of the features of patentable novelty that reside in the present invention, including all the features and embodiments that would be treated as equivalents thereof by those skilled in the relevant art. The invention is further described with reference to the following experimental work.

Example 1

Preparation of Gatifloxacin Pentahydrate

The pentahydrate crystalline form is formed spontaneously from any other crystal form of gatifloxacin in equilibration in water at room temperature. A 1-g sample of gatifloxacin hemihydrate, prepared as described in U.S. Patent No. 5,880,283, is suspended in 5 mL of water and stirred 24 hours at room temperature. The suspension is filtered with gentle suction and partially dried under suction for 2 hours. The resultant cake is further dried in a current of air at ambient pressure, temperature and humidity for 16 hours. The final product was analyzed by powder x-ray diffraction (FIG. 3), differential scanning calorimety (FIG. 4), thermogravimetric analysis (FIG. 5), and KF titration to confirm that it was the pentahydrate crystalline form of gatifloxacin.

FIG. 3 shows the powder x-ray diffraction pattern of gatifloxacin pentahydrate.

FIG. 4 shows the differential scanning calorimetry analysis of gatifloxacin pentahydrate.

FIG. 5 shows the thermogravimetric analysis of gatifloxacin pentahydrate.

Example 2

Large Scale Production of Gatifloxacin Pentahydrate

A 9.5-mg sample of gatifloxacin pentahydrate prepared as in Example 1 was ground with 0.01 mL of water in a mortar and pestle and transferred in 0.1 mL of water to a flask containing 1.10 g of gatifloxacin sesquihydrate. Gatifloxacin sesquihydrate was prepared as described in U.S. Patent No. 5,880,283. One mL of water was added and the mixture stirred for one hour at room temperature. Microscopic examination revealed partial conversion of the rectangular platelets characteristic of the sesquihydrate to the needles characteristic of the pentahydrate. This seed mixture, which had become too thick to flow, was diluted with 1 mL of water and added to a suspension of 599 g of gatifloxacin sesquihydrate in 600 mL of water. An additional 1800 mL of water was added, and the mixture was stirred gently at room temperature for 64 hours. Microscopic examination showed only needles, typically 1x40 to 3x75 micrometers. The mixture, which had the consistency of heavy cream, was filtered with gentle suction and partially dried in the funnel with the suction continually running for 23 hours. The resultant cake, which had the consistency of cream cheese, was sliced and dried at room temperature in a current of air at RH 50-60% for 28 hours. The solid (679 g) was passed through a 20 mesh screen to yield 666 g of powder. Further drying under ambient conditions produced no further weight loss. The final product had a water content of 19.4% by KF titration as expected for the pentahydrate (calculated 19.3%). The powder x-ray diffraction pattern confirmed that the product was gatifloxacin pentahydrate. Thermogravimetric analysis and differential scanning calorimetry also confirmed the pentahydrate form of the product.

Example 3

Typical Composition of Gatifloxacin Pentahydate 100 mg Powder For Suspenion

Gatifloxacin pentahydrate for oral suspension was prepared by combining the following ingredients in the amounts specified:

Ingredient	Amount per 5 gram preparation
Gatifloxacin Pentahydrate	107 mg*
Microcrystalline cellulose and sodium carboxymethylcellulose Avicel® RC-591	50.0 mg
Methyl cellulose and sodium carboxymethylcellulose Methocel A4M Premium®	12.5 mg
Sucrose	1000 mg
Flavoring agent, preservative	As needed

*Equivalent to 100 mg of gatifloxacin /5 g suspension.

Avicel® RC-591 is available from FMC Corporation

Methocel A4M Premium® is available from Dow Chemical Co.

The ingredients were added in the order given and gently mixed. The resulting mixture was sealed in a suitable container. In use, the contents are combined with 3.8 g of water and shaken well to effect the suspension.

Example 4

Typical Composition of Gatifloxacin Pentahydrate 400 mg Tablets

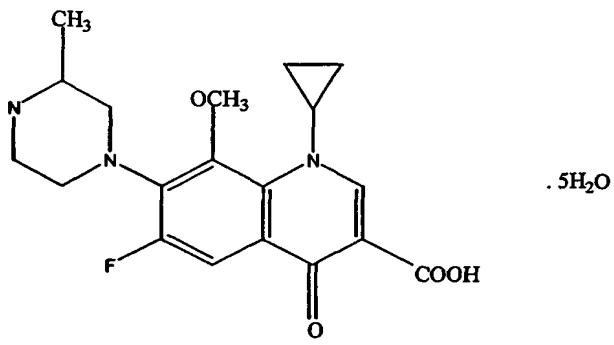
Composition	Grams Per Tablet
Gatifloxacin pentahydrate	0.428*
Microcrystalline cellulose	0.138
Sodium starch glycolate	0.024
Magnesium stearate	0.009
Total Tablet Weight	**0.600**

*Equivalent to 400 mg of gatifloxacin

CLAIMS

We claim:

1. Crystalline gatifloxacin pentahydrate represented by the formula



and characterized by single crystal parameters approximately equal to the following:

Cell dimensions
a=9.339(1) angstrom alpha= 106.55(2) degrees
b=13.556(3) angstrom beta= 91.93(1) degrees
c=9.269(1) angstrom gamma=100.44(1) degrees
V=1101.7(7) cubic angstrom
Space group: P1bar
Triclinic
Molecules/unit cell= 2
Density (calculated) (g/cubic cm)= 1.403

2. Crystalline gatifloxacin pentahydrate in accordance with Claim 1, highly homogeneous with respect to other crystalline forms of gatifloxacin.

3. Crystalline gatifloxacin in accordance with Claim 2, containing no detectable amounts of said other gatifloxacin crystalline forms as determined by the powder x-ray diffraction technique.

4. A process for the preparation of highly homogenous crystalline gatifloxacin pentahydrate which comprises equilibrating gatifloxacin in any crystalline form in water at room temperature until highly homogenous gatifloxacin pentahydrate is formed.

5. A process according to claim 4 wherein there is added to the water suspension of the gatifloxacin seed crystals of crystalline gatifloxacin pentahydrate.

6. A pharmaceutical composition which comprises as an active ingredient an amount of crystalline gatifloxacin pentahydrate as claimed in Claim 2 and one or more pharmaceutically acceptable carriers, excipients or diluents.

7. A pharmaceutical composition in accordance with Claim 6, wherein said composition is a solid dosage form for oral administration.

8. A pharmaceutical composition in accordance with Claim 6, wherein said composition is a powder intended for suspension in water for oral administration.

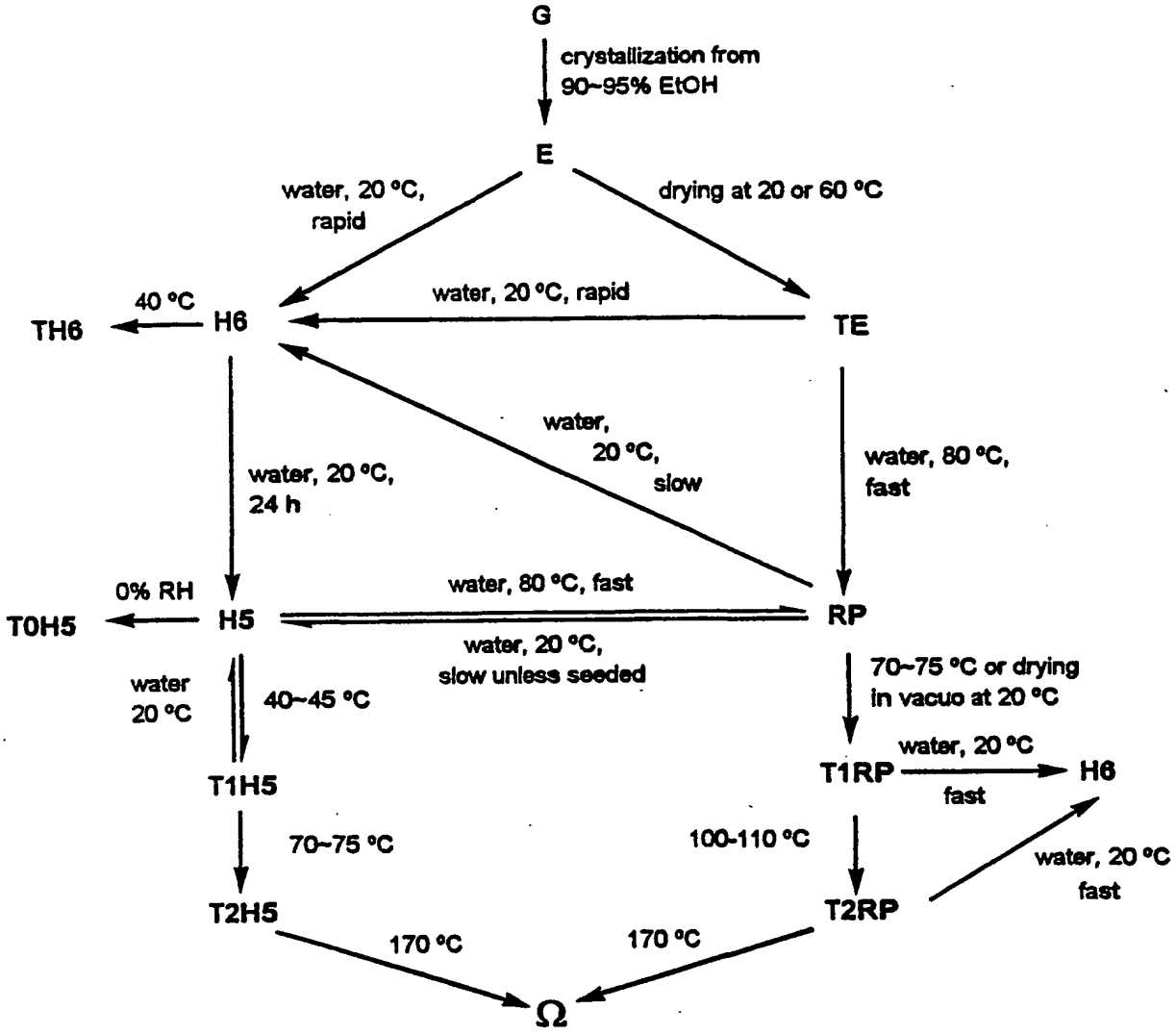
9. A pharmaceutical composition in accordance with Claim 6, wherein said composition is a ready to use suspension in water for oral administration.

10. A method for treating infections which comprises administering to a mammal in need thereof an effective amount of gatifloxacin pentahydrate as claimed in Claim 2.

11. A method in accordance with Claim 10 wherein crystalline gatifloxacin pentahydrate is administered parenterally.

12. A method in accordance with Claim 10 wherein the crystalline gatifloxacin pentahydrate is administered orally.

Summary of gatifloxacin crystal forms and their interrelationships



G	Gatifloxacin
E	Ethanolate, six-sided platelets, gigantic solvent channels, very unstable in absence of mother liquor
TE	Transformed (desolvated) E, approximate hemihydrate, probably contains some T2RP
RP	Rectangular plates, sesqui~dihydrate
T1RP	Transformed RP
T2RP	Transformed T1RP, hemihydrate (monohydrate half occupied)
H5	Pentahydrate, needles or rods or "wheat sheaves"
T0H5	Transformed H5 at 0% RH
T1H5	Transformed H5, monohydrate
T2H5	Transformed T1H5
H6	Hexahydrate, rods
TH6	Transformed H6
Ω	High-temperature form

(Single crystal X-ray structures have been determined for the underlined forms)

FIG. 1

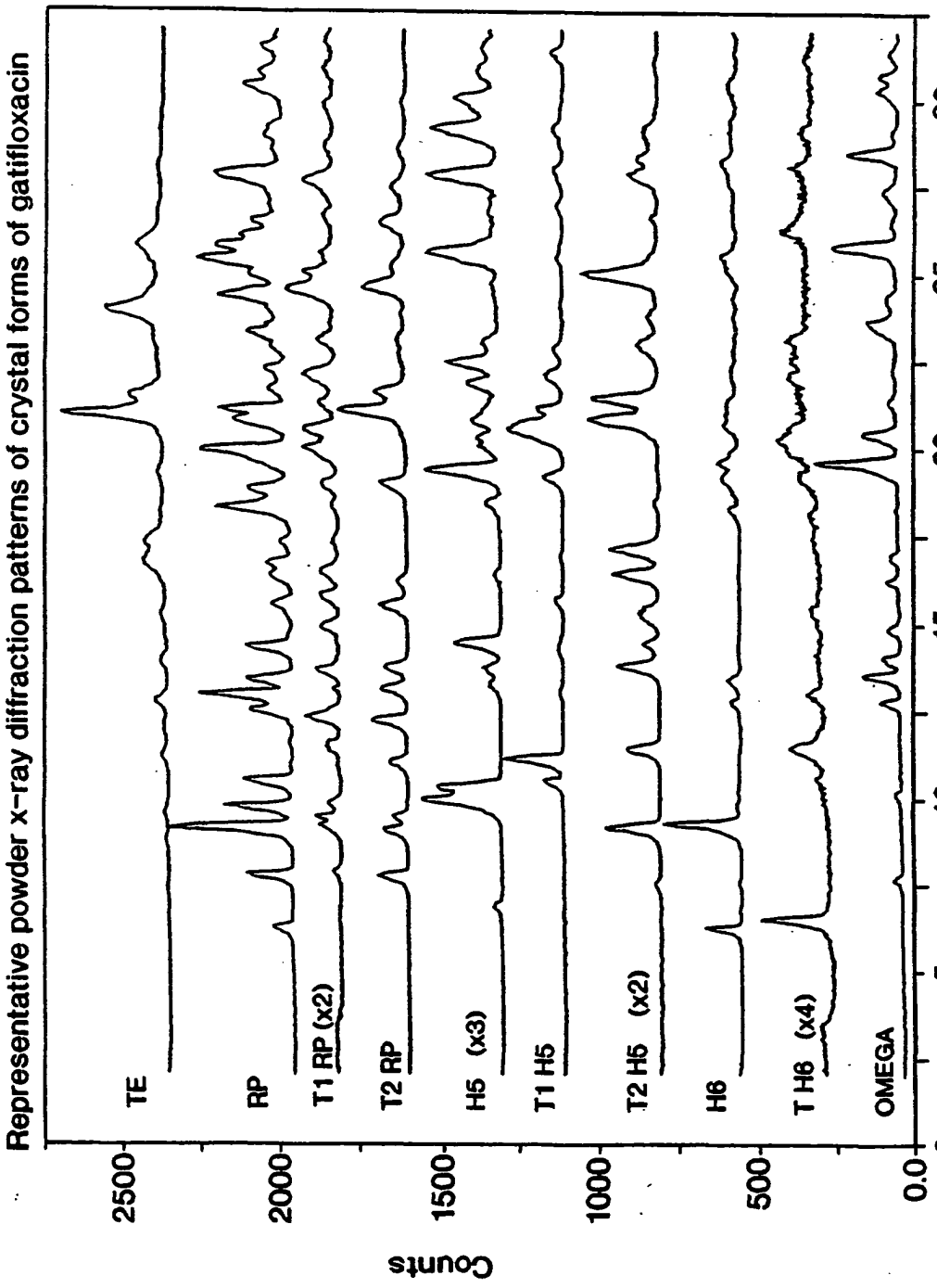


FIG. 2

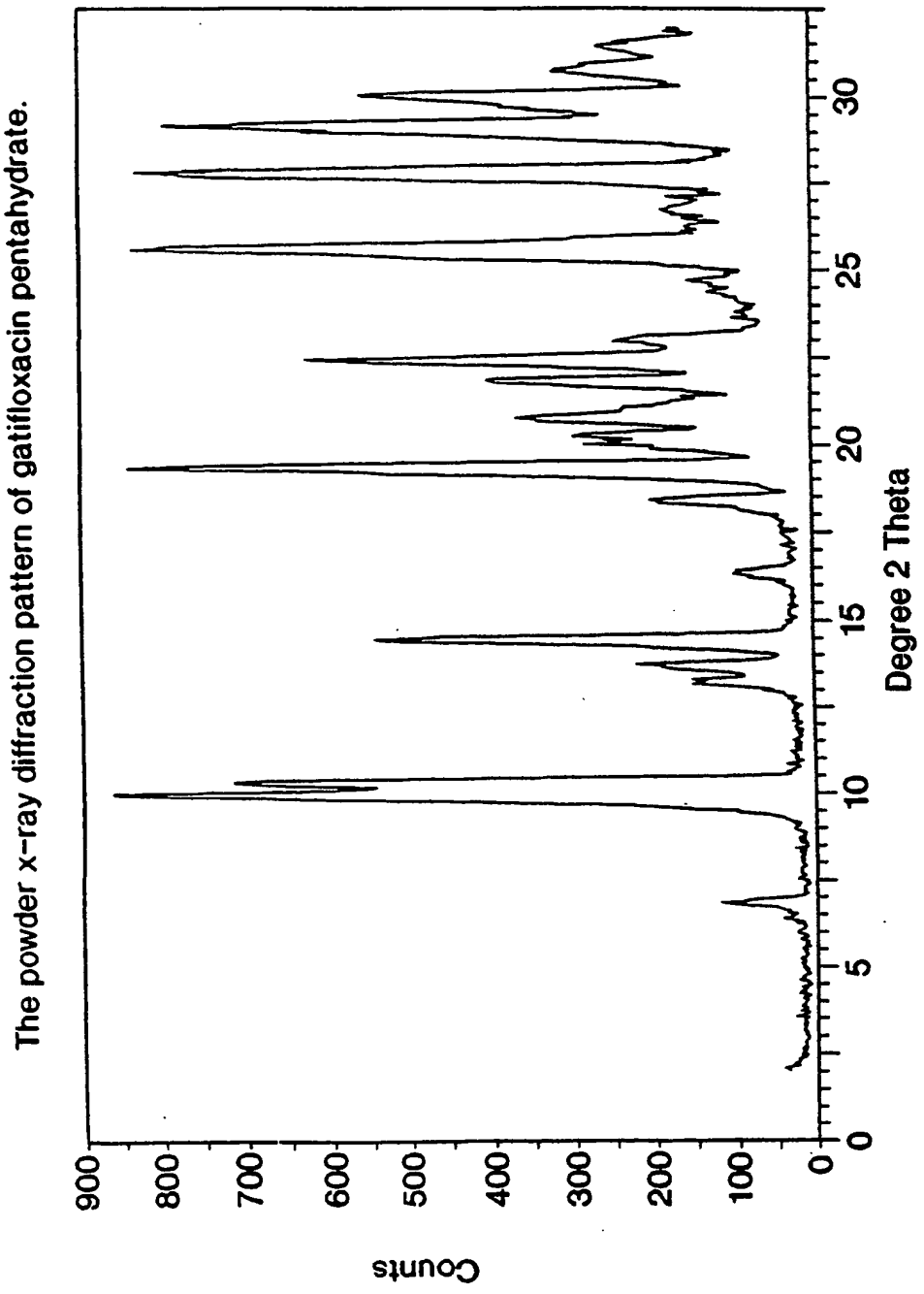


FIG. 3

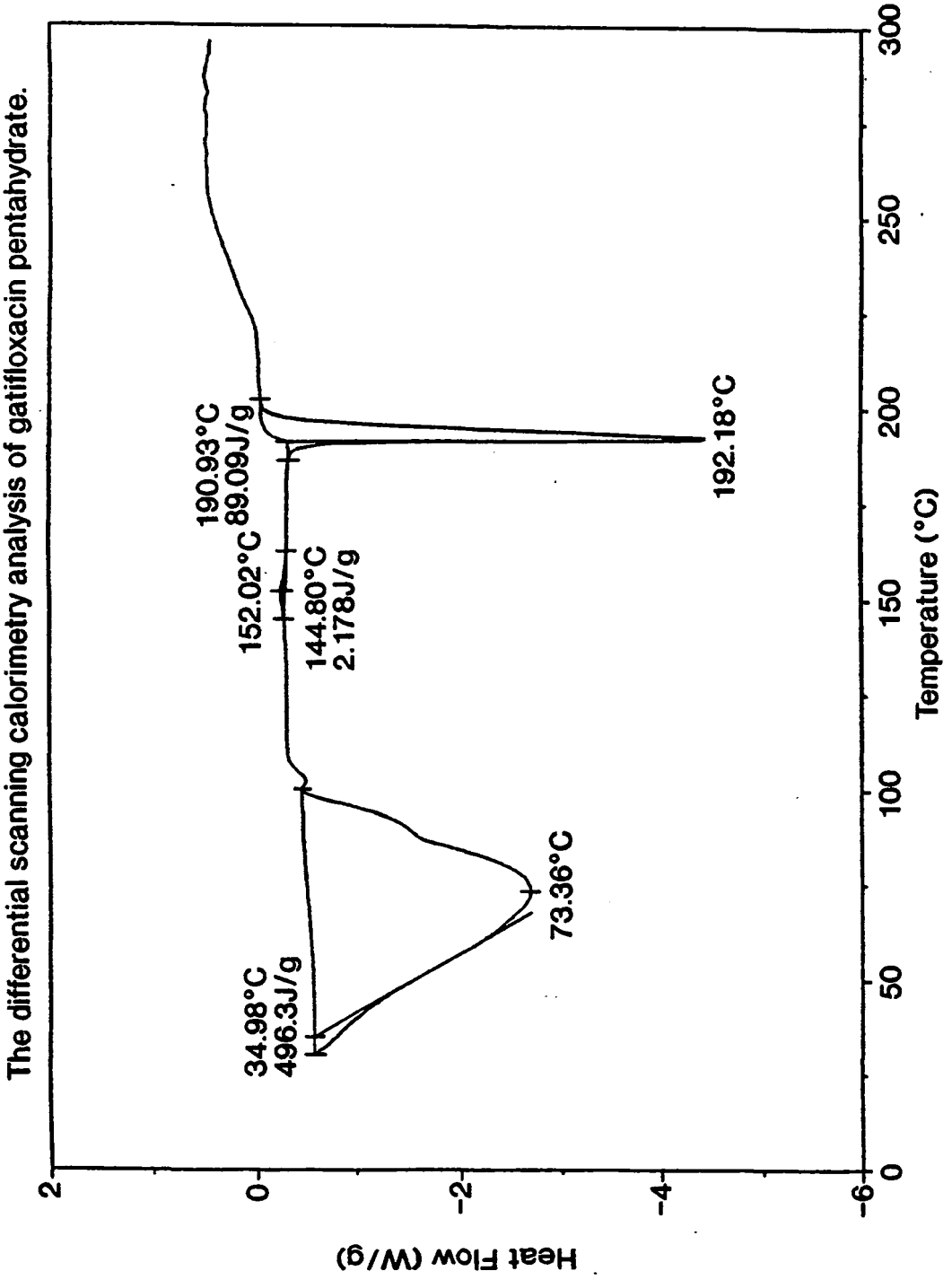


FIG. 4

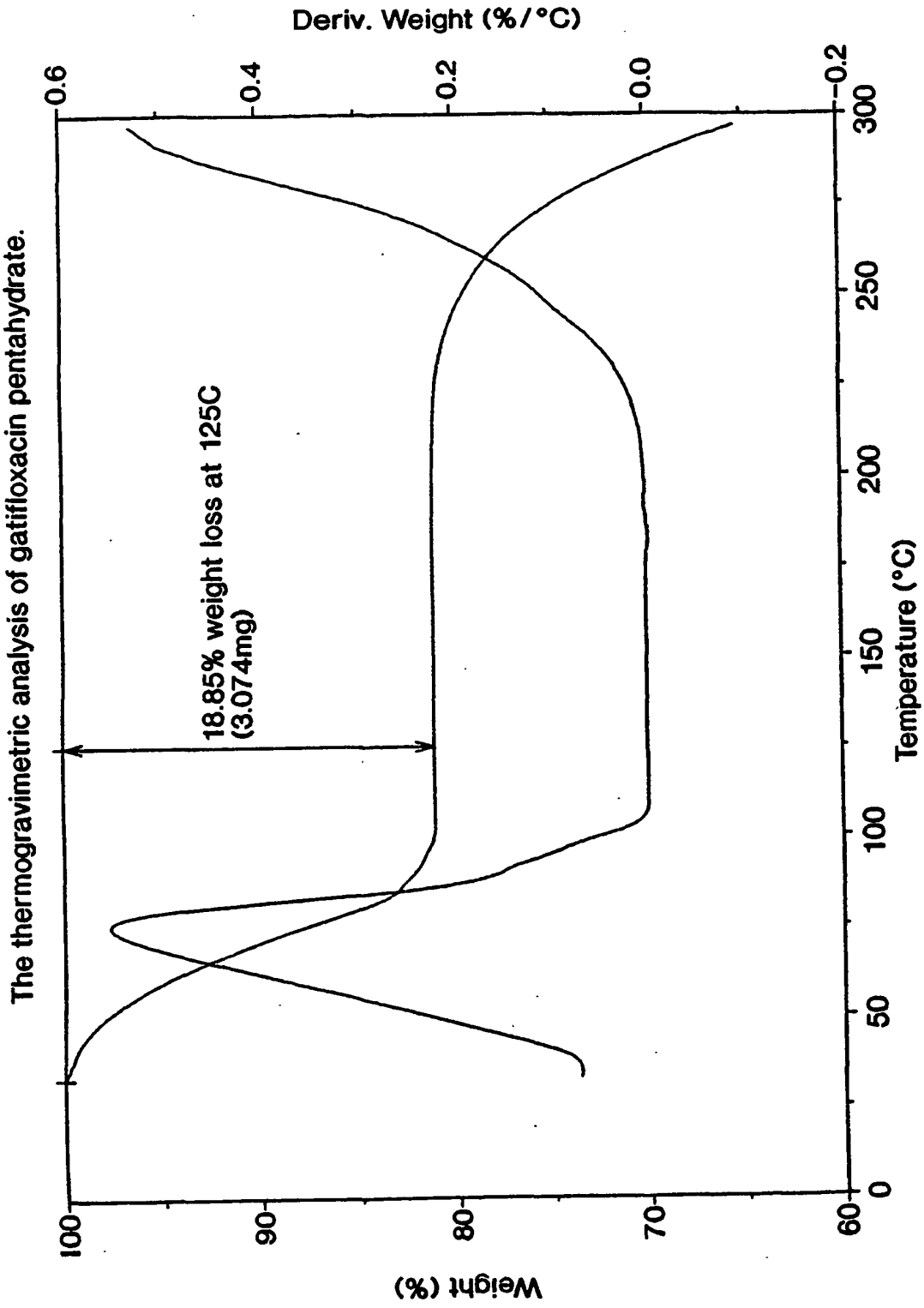

Deriv. Weight (%/°C)
0.6
0.4
0.2
0.0
-0.2
The thermogravimetric analysis of gatifloxacin pentahydrate.
18.85% weight loss at 125C
(3.074mg)
Weight (%)
100
90
80
70
60
0
50
100
150
200
250
300
Temperature (°C)

FIG. 5

INTERNATIONAL SEARCH REPORT

Inter d application No.
PCT/US01/26120

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/496; C07D 401/00.
US CL :514/253.08; 544/363.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/253.08; 544/363.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE STRUCTURE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,043,450 A (MASUZAWA et al.) 27 August 1991, see entire document.	1-12
A	US 5,880,283 A (MATSUMOTO et al.) 09 March 1999, see entire document.	1-12
A,E	US 6,291,462 B (BARTHOLOMAEUS et al.) 18 September 2001, see entire document.	1-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	EMILY BERNHARDT Janice Ford for
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

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